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Scavenging of Tc(V) Formed by I. T. in $^{95m}TcO_4^-$ Solutions#

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Isomeric transition / $^{95m}TcO_4^-$ / $^{95g}Tc(V)$ *complexes*

Abstract

The chemical effects of the I. T. of ^{95m}Tc in $^{95m}TcO_4^-$ have been studied in chelating ligand solutions. At high pH and at high concentration of 1,4,8,11-tetraazacyclotetradecane and 1,4-dithia-8,11-diazacyclotetradecane, the retention of ^{95g}Tc is about 20% and the unretained ^{95g}Tc appears preponderantly (ca. 73%) as $[TcO_2L]^+$ complexes. In glucoheptonate solution, the ^{95g}Tc retention remains practically the same (22%) but the unretained ^{95g}Tc is found in high proportion (73%) as [TcO bis(glucoheptonate)]$^-$. The added ligands are very good scavengers for $^{95g}Tc(V)$.

A comparison is made between ^{95g}Tc species formed by the I. T. in $^{95m}TcO_4^-$ and ^{99m}Tc species resulting from the chemical reduction of $^{99m}TcO_4^-$.

1. Introduction

The chemical effects of the I. T. of ^{95m}Tc in $M^{99(95m)}TcO_4^-$ (M = Li, K) in solution have been studied previously [1]. It has been found that the ^{95g}Tc retention value was dependent on the pertechnetate and on the Tc(IV) carrier concentrations. In the absence of carrier only $^{95g}TcO_4^-$ is found.

The aim of this work is to use chelating ligands as scavengers for reduced ^{95g}Tc species formed by the decay of ^{95m}Tc in carrier free $^{95m}TcO_4^-$ solution. Following ligands are used: 1,4-dithia-8,11-diazacyclotetradecane (cis[14]ane N_2S_2), 1,4,8,11-tetraazacyclotetradecane (cyclam), 1,3-bis(ethylene 1,2-diamino) propane (2,3,2-tet) and α-D-glucoheptonate. As these ligands are excellent complexing agents for $Tc(V)O_2^+$ or $Tc(V)O^{3+}$ ions, they can scavenge these species before they are oxidized back to pertechnetate by traces or oxygen and/or water. In recent years, the complexes of Tc(V) with these ligands have been synthesized [2–6], and they are known to be stable.

2. Experimental

The 2,3,2-tet, cis[14]ane N_2S_2 and cyclam ligands were kindly provided by the Institutes of Inorganic Chemistry, the first from ETH-Zürich and the others from Basel. Analytical grade calcium glucoheptonate (Fluka) was used without further purification.

Preparation of $^{95m}TcO_4^-$

The ^{95m}Tc was obtained by irradiation of molybdenum powder with 25 MeV protons in the SIN cyclotron at Villigen, Switzerland. The target was dissolved in 30% H_2O_2 using a reflux system and ^{95m}Tc was separated as TcO_4^- by several extractions with MEK from a basic (KOH) solution [7]. The ligand solution of known concentration and pH was added to the solution of $K^{95m}TcO_4^-$ and sparged with nitrogen gas. The ^{95m}Tc activity (5 μCi) was kept constant in all samples. Generally the pH was adjusted with phosphate buffer solutions. For pH values lower than 4 or higher than 11, adjustment was made with 0.1 M H_3PO_4 and 0.1 M NaOH respectively. The concentrated solutions ($c > 10^{-2}$ M) of cis[14]ane $N_2S_2 \cdot 2$ HCl at pH 9.5 were prepared with 0.1 *M* NaOH. A solution of 5×10^{-2} M glucoheptonate in water (pH = 5.8) was used in the experiments.

Labelling with ^{99m}Tc

Labelling was performed in a penicillin vial containing an aqueous ligand solution to which were added successively a phosphate buffer (pH 5–10), the ^{99m}Tc activity (3 mCi) in physiological saline (generator eluate) solution and $SnCl_2$ in 0.1 M HCl [2–6]. Values of pH lower than 4 or higher than 11.5 were obtained by addition of 0.1 M HCl or 0.1 M NaOH respectively. The labelling of the glucoheptonate with ^{99m}Tc was accomplished using 5×10^{-2} M glucoheptonate at pH 5.8 in the presence of a large excess of $SnCl_2$ [4].

Separation procedure

The separation of the technetium species was achieved by high voltage electrophoresis with Schleicher-Schüll paper N° 2040 B and 0.05 M or 0.1 M phosphate buffer at pH 8.5 as supporting electrolyte. For samples at pH 4, the electrolyte 0.05 M NaH_2PO_4 was used. A voltage of 2000 V was applied for 30 min. For samples of ^{95m}Tc the paper was cut into small pieces before activity was measured.

Activity measurements

^{99m}Tc ($T_{1/2}$ = 6 h) was measured with a TLC linear analyser; the system consisted of a 3″ × 3″ NaI(Tl) detector arranged to scan the electrophoresis paper (velocity: 2–5 cm/min); the data were collected on a HP 86B computer for further processing. ^{95m}Tc ($T_{1/2}$ = 61 d) and ^{95g}Tc ($T_{1/2}$ = 20 h) were measured with a high resolution Ge/Li detector connected to an Ortec multi-channel analyser. The activities of ^{95m}Tc and ^{95g}Tc were obtained measuring the γ-rays of 835 keV and 766 keV respectively.

3. Results

The ^{95m}Tc decay in $^{95m}TcO_4^-$ in solutions of cis[14] ane N_2S_2, cyclam and 2,3,2-tet leads to the formation of $^{95g}TcO_4^-$, two cationic species and a neutral product. The production yields of these species are essentially dependent on the pH of solution. It has been found that the

Dedicated to Professor Dr. P. Lerch on the occasion of his 60th birthday

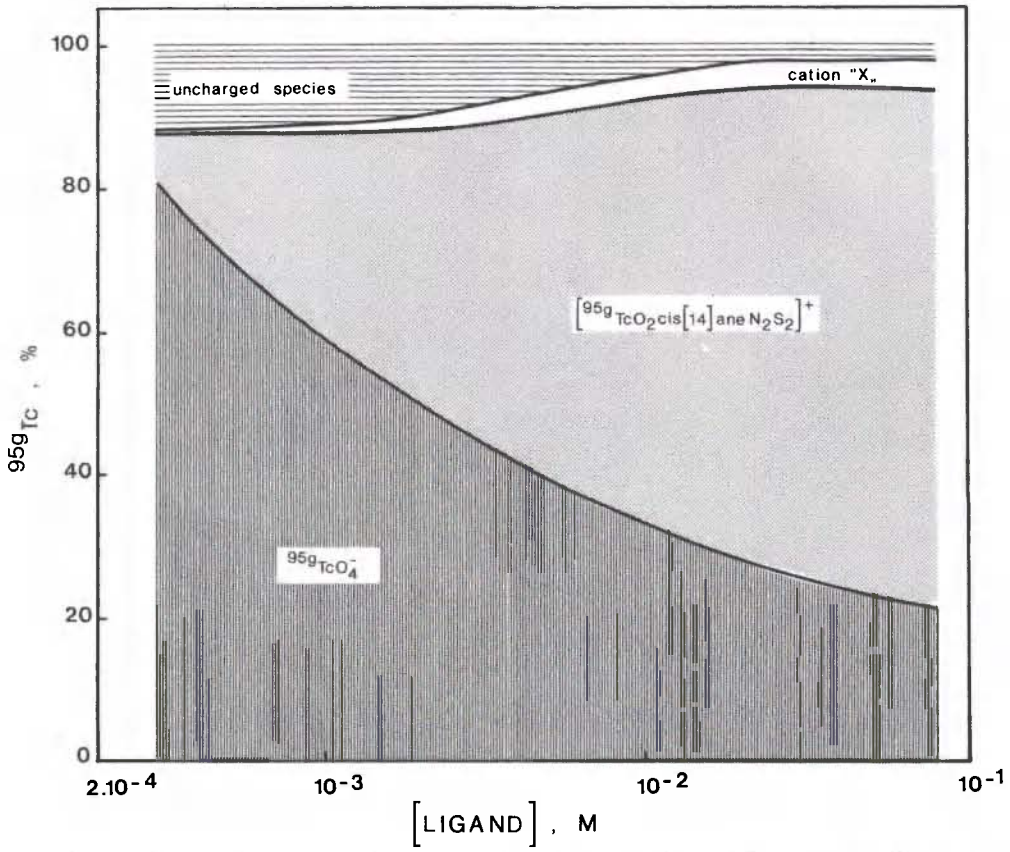

Fig. 1. ^{95g}Tc distribution for $^{95m}TcO_4^-$ in cis[14]ane N_2S_2 solution as a function of cis[14]ane N_2S_2 concentration; pH = 9.5; storage = 293 K, N_2.

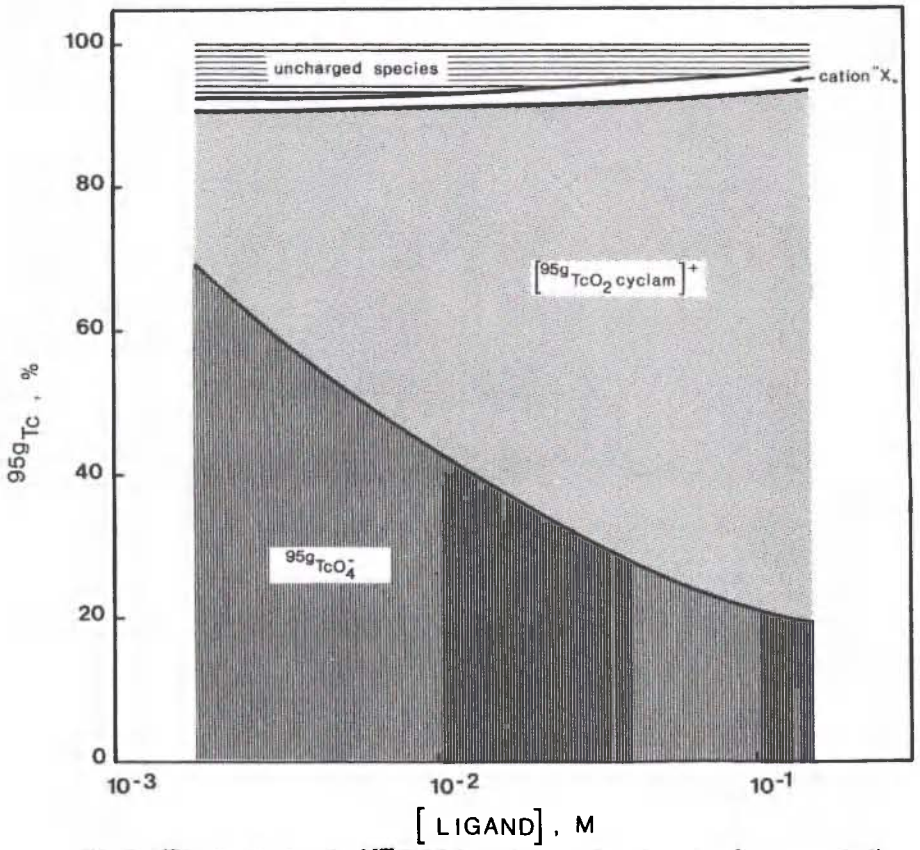

Fig. 2. ^{95g}Tc distribution for $^{95m}TcO_4^-$ in cyclam as a function of cyclam concentration; pH = 11.0; storage = 293 K, N_2.

Table 1. Electrophoretic migration distance (cm) of Tc-complexes

Ligand complexed to ^{99}Tc, ^{99m}Tc, ^{95g}Tc	$[TcO_2L]^+$	Cation "X"	Conditions
Cis 14 ane N_2S_2 Cyclam 2, 3, 2-tet	9 ± 1	3 ± 1	Phosphate buffer pH = 8.5 2000 V, 10 mA, 30 nm

reduction of $^{99m}TcO_4^-$ with Sn^{2+} in the presence of the same ligands at pH = 11.5 leads to the formation of 96% $[TcO_2L]^+$, 3% cation "X" and 1% neutral product. At lower pH, the yield of the latter increases whereas the proportion of cation "X" does not change significantly. The highest yield (10%) of the latter species is found at pH 4.5. The electrophoretic migration distances of cationic complexes obtained either by I.T. in $^{95m}TcO_4^-$ or by $^{99m}TcO_4^-$ reduction with $SnCl_2$ are shown in Table 1. For comparison purpose, the migration distances of the corresponding ^{99}Tc-complexes are also given. It appears that I.T. in $^{95m}TcO_4^-$ gives the $[^{95g}TcO_2L]^+$. The influence of ligand concentration on the ^{95g}Tc distribution in the $^{95m}TcO_4^-$/cis[14]ane N_2S_2 at pH 9.5 is shown in Fig. 1. The increase of ligand concentration favours the formation of $[^{95g}TcO_2$ cis[14]ane $N_2S_2]^+$ complex and this is reflected in the decrease of the $^{95g}TcO_4^-$ yield; the total amount of cation "x" and uncharged species is not significantly affected.

The distribution of ^{95g}Tc-chemical species as a function of cyclam concentration at pH 11.0 is shown in Fig. 2. The comparison of Fig. 1 and 2 shows that the general trends of the dependence on the [L] in both cis[14]ane N_2S_2 and cyclam solutions are rather similar. However for a given concentration of ligand the proportion of $^{95g}TcO_4^-$ in cyclam is higher than in cis[14]ane N_2S_2 (Fig. 3). The difference between the $^{95g}TcO_4^-$ proportions decreases with the increase of [L] and vanishes for $[L] \sim 1.3 \times 10^{-1}$ M. The yield of $^{95g}TcO_4^-$ is the same at pH 7 and 11. At $c \sim 1.3 \times 10^{-1}$ M, independently of the type of ligand and pH, the yield of $^{95g}TcO_4^-$ is ca. 20% and that of $[^{95g}TcO_2L]^+$ is about 73% (Fig. 4). For cyclam concentrations between 2.5×10^{-2} and 3×10^{-3} M, the behaviour of $[^{95g}TcO_2$ cyclam$]^+$ is the same at pH 7 and 11. At a lower concentration (i.e. 2.3×10^{-3} M), the formation of uncharged product in high amount is concomitant with the rapid decrease of the $[TcO_2$ cyclam$]^+$ fraction (Fig. 4).

The dependence of the $[^{95g}TcO_2L]^+$ yield on the ligand concentration is not surprising since it has already been observed in the complexation of ^{99m}Tc with cyclam at pH 9 or 11 [2]. It is known that macrocyclic ligands such as cyclam and cis[14]ane N_2S_2 are very good complexing agents for $^{99m}Tc(V)$. The yields of $[^{99m}TcO_2$ cyclam$]^+$ and of $[^{99m}TcO_2$ cis[14]ane $N_2S_2]^+$ are higher than 90% when the synthesis is performed at pH 11, but they decreases at lower pH. These findings are apparently in disagreement with the results presented in Fig. 4. However, this difference can be explained taking into account the data obtained in experiments with ^{99m}Tc.

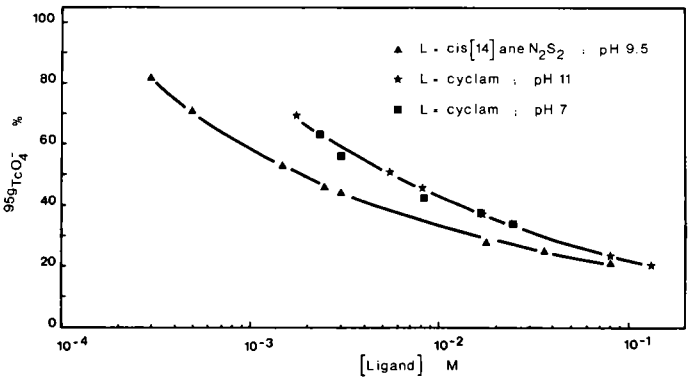

Fig. 3. $^{95g}TcO_4^-$ yield vs. [Ligand].

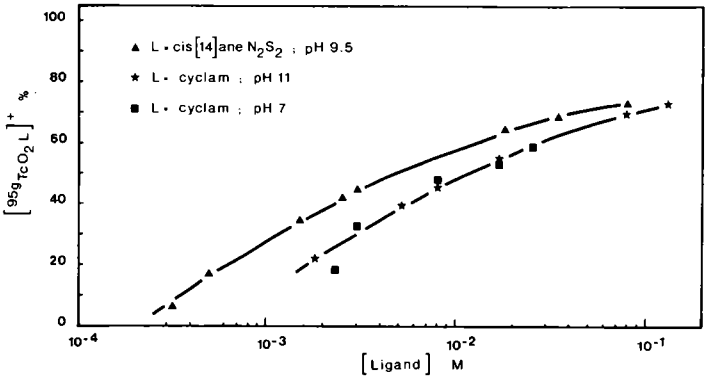

Fig. 4. $[^{95g}TcO_2L]^+$ yield vs. [Ligand].

It has been reported [5] that the $[^{99m}TcO_2$ (2,3,2-tet)$]^+$ complex formed in high yield by the reduction of $^{99m}TcO_4^-$ with Sn^{2+} at pH 11 was not stable in basic solution. In order to avoid the decomposition, the pH was adjusted to 7.5 immediately after the preparation of the complex. The $[^{99m}TcO_2$ cis[14]ane $N_2S_2]^+$ shows a similar behaviour. The decomposition leads to the formation of $^{99m}TcO_4^-$. The lower stability of Tc-dioxo-complexes at high pH explains the results presented in Fig. 4. The lower yield of $[^{95g}TcO_2$ cyclam$]^+$ than that of $[^{95g}TcO_2$ cis[14]ane $N_2S_2]^+$ is due to the more extensive decomposition at pH 11 than at 9.5. Since the latter pH favours the complexation and limits the decomposition, the yield of $[^{95g}TcO_2L]^+$ under these conditions is higher than that obtained at pH 7.

The influence of pH on $[TcO_2$ cis[14]ane $N_2S_2]^+$ yield formed either by the decay of ^{95m}Tc in $^{95m}TcO_4^-$ or by the reduction of $^{99m}TcO_4^-$ with $SnCl_2$ is shown in Fig. 5. The same complex yield is obtained up to pH 7 in both cases. Above pH 7, the difference in the behaviour of the two complexes (curves 1 and 2) appears to be due

Table 2. ^{95g}Tc- and ^{99m}Tc-products formed by I.T. in $^{95m}TcO_4^-$ and by reduction of $^{99m}TcO_4^-$ in presence of macrocyclic ligands

pH	Ligand Type	Ligand Conc. (M)	TcO_4^- %	$[TcO_2L]^+$	Cation "X" %	Uncharged species %
A. ^{95g}Tc-species resulting from I.T. in $^{95m}TcO_4^-$						
4.0	Cyclam	2×10^{-2}	27.4 ± 0.5	–	12.0 ± 0.4	60.6 ± 0.1
12.5	Cyclam	2×10^{-2}	95.6 ± 1.0	–	–	4.4 ± 0.8
7.5	Cis[14]ane N_2S_2	2×10^{-2}	25.6 ± 0.3	62.0 ± 0.2	5.9 ± 0.5	6.5 ± 0.6
12.5	Cis[14]ane N_2S_2	2×10^{-2}	94.4 ± 0.3	–	–	5.6 ± 0.7
B. ^{99m}Tc-species formed by reduction of $^{99m}TcO_4^-$ with $SnCl_2\cdot2H_2O$[a]						
4.5	Cis[14]ane N_2S_2	5×10^{-3}	–	–	9.7 ± 1.4	90.3 ± 1.2
7.0	Cis[14]ane N_2S_2	5×10^{-3}	–	58.8 ± 1.1	5.1 ± 0.7	36.1 ± 1.5
12.5	Cis[14]ane N_2S_2	5×10^{-3}	2.8 ± 0.3	86.0 ± 0.3	5.0 ± 0.3	6.4 ± 0.2
12.5[b]	Cis[14]ane N_2S_2	5×10^{-3}	98.5 ± 0.6	–	–	1.5 ± 0.4

a) solutions analyzed after 5 mn. b) solutions analyzed after 24 h.

Table 3. Influence of O_2 on the yields of ^{95g}Tc-species formed in $^{95m}TcO_4^-$ + L solution
L: [Cyclam] = 1.7×10^{-3} M, pH = 11; [2,3,2-tet] = 1.1×10^{-2} M, pH = 10

L	atmosphere	$^{95g}TcO_4^-$ %	$^{95g}TcO_2L^+$ %	^{95g}Tc-cation "X" %	^{95g}Tc-uncharged species %
Cyclam	N_2	37.2 ± 0.2	55.0 ± 1.1	1.8 ± 0.2	6.0 ± 0.3
	O_2	40.2 ± 0.6	51.0 ± 0.1	5.1 ± 0.6	3.7 ± 0.4
2,3,2-tet	N_2	36.4 ± 3.3	60.7 ± 0.1	2.4 ± 0.3	0.5 ± 0.1
	O_2	48.2 ± 2.1	40.5 ± 3.2	8.5 ± 1.8	2.8 ± 0.7

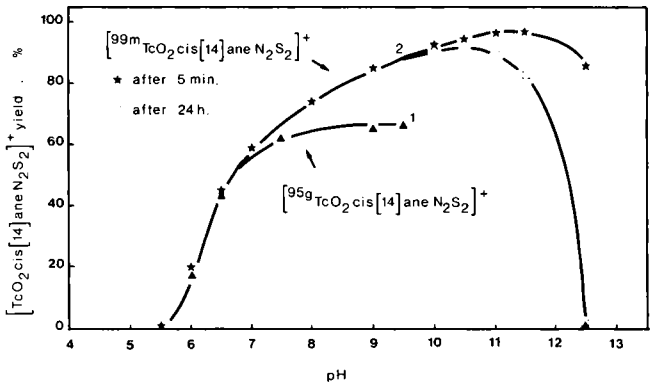

Fig. 5. $[TcO_2$ cis[14]ane $N_2S_2]^+$ yield vs. pH.
1 – $^{95m}TcO_4^-$, [Ligand] = 1.8×10^{-2} M
2 – $^{99m}TcO_4^- + Sn^{2+}$, [Ligand] = 5×10^{-3} M.

to the differences in the ageing of complex solutions. The storage of the products obtained by I.T. is much longer than that of products resulting from the reduction process; in the latter case, the storage is limited by the half-life of ^{99m}Tc. Nevertheless, it can be seen that even after one day the complex yield decreases in solutions of pH higher than 10. The fact that the cationic complexes formed in both processes have the same behaviour shows that the I.T. in $^{95m}TcO_4^-$ leads to $[^{95g}TcO_2L]^+$. The effect of pH on the yields of the chemical species formed either by isomeric transition or by reduction is shown in Table 2. At low pH, besides the $^{95g}TcO_4^-$, only uncharged and cation "X" are formed and at high pH, all species are practically oxidized to TcO_4^-. An interesting result is that, at pH 4.5 and 7, the oxydation of ^{99m}Tc-species to $^{99m}TcO_4^-$ does not occur.

The effect of oxygen on the chemical distribution of ^{95g}Tc is shown in Table 3. The ^{95g}Tc distribution in a solution of cyclam is much less affected by oxygen than in 2,3,2-tet solution. The complex formed with 2,3,2-tet is expected to be less stable than with cyclam because of the increasing number of chelating rings and of the macrocyclic effect in the latter.

On the bases of available data, it appears that dioxo complexes of ^{99m}Tc(V) are formed with neutral ligands whereas with negatively charged ligands, five-coordinated monooxo complexes are formed. As a consequence, the glucoheptonate has been used as scavenger for the $^{95g}TcO^{3+}$ species. The results of ^{95m}Tc decay in $^{95m}TcO_4^-$/glucoheptonate are shown in Fig. 6. For comparison, the proportions of ^{99m}Tc-species formed by the reduction of $^{99m}TcO_4^-$ with $SnCl_2$ in presence of glucoheptonate are also given. The ^{95g}Tc species are the same as those resulting from the reduction of $^{99m}TcO_4^-$. They show the same electrophoretic migration and the same behaviour with respect to the pH of the solution and to the concentration of the ligand. The [TcObis(glucoheptonate)]$^-$ is formed in high yield, 90% and 73% with ^{99m}Tc and ^{95g}Tc respectively. The value of ^{95g}Tc retention is ca. 22%.

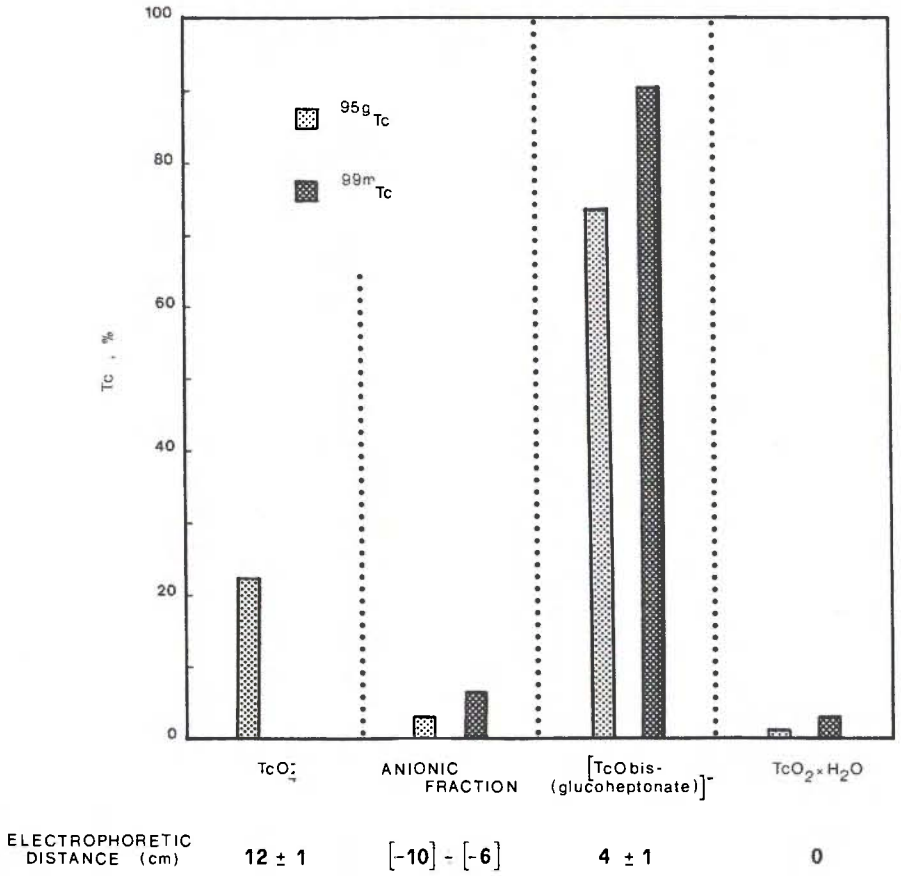

Fig. 6. ^{95g}Tc- and ^{99m}Tc-products formed by I. T. in $^{95m}TcO_4^-$ and by reduction of $^{99m}TcO_4^-$ with Sn^{2+} in glucoheptonate solution conc. = 5×10^{-2} M, pH = 5.8.

4. Discussion

The products of isomeric transition in $^{95m}TcO_4^-$ solutions containing the ligands, besides $^{95g}TcO_4^-$, are the same Tc(V) complexes as can be produced by $SnCl_2$ reduction of $^{99m}TcO_4^-$ in the presence of complexing agents. Figs. 1 and 2 suggest that at high enough concentration of ligands, only about 20% of the ^{95g}Tc appears as TcO_4^-. In fact the solubility of the ligands limits the accessible concentrations. The curves suggest that there is a competition between oxidation of nascent ^{95g}Tc species by traces of oxygen and/or water, and complexation by the ligands.

Let us assume that a fraction "a" from ^{95g}Tc inevitably gives TcO_4^- (it could be either true retention of ^{95g}Tc(VI)). The $(1-a)$ part available to form another chemical species is found as ^{95g}Tc(V). The latter is participating in two reactions: 1) oxidation by air and/or water to TcO_4^- and 2) complexation by ligand. The rate of the first reaction is equal to $k'(1-a)$ and the rate of the second is $k''(1-a)[L]$, where [L] is the concentration of complexing scavenger.

Now if "x" is the measured fraction of $^{95g}TcO_4^-$ then the fraction $(1-x)$ of ^{95g}Tc(V) will be given by:

$$(1-x) = (1-a)\frac{k''(1-a)[L]}{k'(1-a)+k''(1-a)[L]}$$

which can also be written

$$\frac{1}{1-x} = \frac{1}{1-a} + \frac{k'}{k''(1-a)[L]}$$

where x and [L] are experimental quantities.

This expression is valid if the ^{95g}Tc(V) is formed either directly as Tc(V) or by the oxidation of Tc(IV) or some lower oxidation states.

By plotting $1/(1-x)$ against $1/[L]$ where L is cyclam and cis[14]ane N_2S_2 (Fig. 7, straight lines 1 and 2 respectively), one can determine the intercept $1/(1-a)$. The a value is found equal to 0.215.

The slope of the plot gives $k'/k''(1-a)$. By calculating the ratio between the slopes for cyclam and cis[14]ane N_2S_2 one finds

$$\frac{k''\text{cis[14]ane } N_2S_2}{k''\text{cyclam}} = \frac{4.36 \times 10^{-3}}{1.48 \times 10^{-3}} \approx 3$$

i. e. the complexation of Tc(V) by cis[14]ane N_2S_2 is about 3 times faster than by cyclam.

The I. T. in $^{95m}TcO_4^-$ in solution of ^{99}Tc(IV) carriers at pH 3 led to the formation of the ^{95g}Tc in tetravalent state [1]. The yield of the latter was dependent on the carrier concentration; it reached ca. 80% for $c = 4.5 \times 10^{-3}$ M.

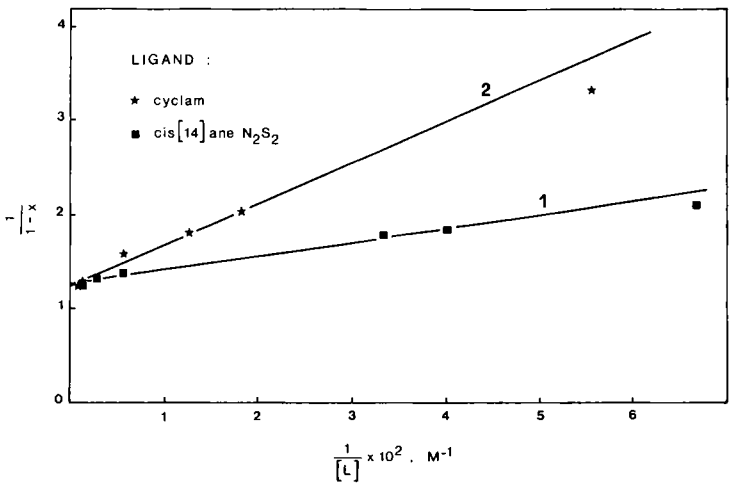

Fig. 7. Plot of $1/(1-x)$ versus $1/[L]$ (x: $^{95g}TcO_4^-$, %).

In this study the I.T. appears to produce $^{95g}Tc(V)O_2^+$ or $^{95g}Tc(V)O^{3+}$ species which are liable to the scavenging by organic ligands. The isomeric transition is highly internally converted ($\alpha = 7 \times 10^4$ [8]); it is expected that many, if not all, of the events would lead to the fragmentation of the parent molecule. The precise mode of formation and the identity of the precursors of ^{95g}Tc species in solutions are not known. All these results suggest that the Auger cascade leads in most events ^{95g}Tc with an oxidation state of +4 or less. An efficient reaction reconverting the reduced ^{95g}Tc species to TcO_4^-, in absence of appropriate scavengers, occurs. It is reasonable to assume the participation of oxidizing radiolytic products ($OH^\cdot$, $HO_2^\cdot$) in this process. The majority (three or four) of the Auger electrons have kinetic energies less than 2 keV [9], so that there will be a localized radiolysis of the aqueous medium in the close vicinity of the nascent ^{95g}Tc. If the ligand molecules are inside the radiolytic zone they have a chance to prevent the ^{95g}Tc to react with the oxidizing products. However, as the diffusion rate of the ligand molecule is lower than that of the $OH^\cdot$ radical the efficiency of the Tc interaction with the ligand will be determined by the distance between them. Considering spherical molecules, this mean distance is given by

$$\bar{d} = 2\sqrt[3]{\frac{3}{4\Pi} \times \frac{10^{27}}{N_A M}} \text{ Å}$$

where N_A is the Avogadro number and M the molarity (moles per liter).

At a concentration of 1.3×10^{-1} M, corresponding to a mean distance of 29 Å, ca. 80% of the $^{95g}Tc(V)$ is protected via complexation by the ligand. The dimensions of the reduced technetium ion and of the ligand molecule cannot be estimated. However, the results suggest that both the $^{95g}Tc(V)$ ion radius and the ligand equivalent radius should be close to 14.5 Å.

The fate of the ^{95g}Tc will be determined by the complexing properties and the concentration of the ligand and by the ^{95g}Tc-complex stability. As the cation "X" and the neutral product are formed essentially at low pH the Tc in +4 oxidation state in these species can not be excluded. Unfortunately, neither the structure nor the oxidation state of Tc have been determined at this time. Our work on the isolation of ^{99}Tc-complexes from dilute acid solution and their characterization is now in progress.

Acknowledgements

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